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Factors Associated with N-specific IgG Response in Piglets Experimentally Infected with Porcine Reproductive and Respiratory Syndrome Virus

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Summary and Implications

This study examined serum porcine reproductive and respiratory syndrome virus (PRRSV) N protein-specific IgG levels from sera collected from 464 Large White-Landrace commercial crossbred piglets from three separate experimental infection trials with PRRSV isolate NVSL-97-7895. IgG levels at 42 days post infection (dpi) were measured by fluorescent microsphere immunoassay, herein referred to as total antibody (tAb) response. tAb levels were assessed for an association with different disease-related traits, the presence of a heritable genetic component, and for genomic regions associated with tAb response. tAb response was negatively associated with viral load (VL) and weight gain from 28-42 dpi (WG) and positively associated with virus rebound (REB) and neutralizing antibody (nAb) levels. Furthermore, tAb response had a heritable genetic component, with a major QTL located on chromosome 7 in the major histocompatibility complex (MHC), whereby heterozygous individuals had a lower tAb response and increased weight gain from 28-42 dpi. These results suggest that genetic selection for tAb response may be useful for selecting for pigs that have increased resistance or reduced susceptibility to PRRSV.

Introduction

Porcine reproductive and respiratory syndrome (PRRS) affects all stages of swine production and costs the U.S. pork industry $664 million annually. High mutation rates and the variability of PRRSV have encumbered vaccine, biosecurity, and eradication efforts. The goal of the PRRS Host Genetics Consortium (PHGC) is to identify genomic markers and pathways associated with host anti-PRRS response, which can be used for genetic selection of pigs for increased resistance or reduced susceptibility.

Boddicker et al. (2012) identified a single nucleotide polymorphism (SNP) on chromosome 4 (WUR10000125), for which the favorable allele (B) was associated with reduced viral load (VL) and increased weight gain (WG) following experimental infection with the NVSL-97-7895 PRRSV isolate. Serum level of immunoglobulin G (IgG) likely contributes to observed host responses when infected with PRRSV. The objective of this study was to identify factors associated with tAb response, determine whether a heritable genetic component was present, and perform a Genome-Wide Association Study (GWAS) to identify markers associated with tAb response.

Materials and Methods

The data were from 464 Large White-Landrace crossbred piglets from three separate experimental infection trials of the PHGC. All piglets were experimentally challenged with PRRSV isolate NVSL-97-7895 at 28-35 days of age. Serum samples were periodically collected until 42 dpi and viremia determined by qPCR assays. Serum samples collected at 42 dpi were assayed for tAb response using the fluorescence microsphere immunoassay to detect virus N protein-specific IgG, whereby a negative control was included to adjust for background during analysis. Results, reported as the mean fluorescence intensity (MFI), were obtained from MAGPIX. Viral load (VL) was defined as the area under the curve of Log viremia from 0-21 dpi. A piglet was classified as having a virus rebound (REB) based on statistical evidence of a secondary viremia peak after 21 dpi. Weight gain from 28 to 42 dpi (WG) was assessed also. Neutralizing antibody (nAb) activity was defined as the last 1:2 serial dilution of serum incubated with 200 50% tissue culture infectious doses of PRRSV without cytopathic effects in MARC-145 cells (titer). All piglets were genotyped using the 60k SNP chip.

Analyses were carried out using an animal model in ASReml in order to utilize pedigree information. Variance components were estimated in order to establish the presence of a heritable genetic component to tAb response. The negative control MFI and median sample MFI within each plate were fitted as covariates to control for plate-to-plate variation. Trial and parity of the sow nested within trial were fitted as additional fixed effects. Pen nested within trial, litter, plate, and the genetic effect of pig were included in the model as random effects. To assess the presence of an association with tAb response, VL, REB, WG, and nAb activity were then each separately added to the model. After identification of a SNP associated with tAb in the GWAS (see below), the genotypes at this SNP were added as a fixed effect to the animal model to assess its association with tAb response, nAb activity, VL, REB, and WG.

A genome-wide association study using 60k SNP data was conducted using the BayesB option in GenSel, with the proportion of SNPs with no effect (π) assumed to be 0.99. For this analysis, trial, parity nested within trial, pen nested within trial, and plate were fitted as fixed effects and negative control MFI and median sample MFI were fitted as covariates.

Results and Discussion

The pedigree-based estimate of heritability for tAb was 18±14%. Pigs that did not experience virus rebound had a 1216±573 lower MFI (p=0.036), and each additional nAb titer was associated with a 360±132 unit increase in MFI (p=0.007). A one standard deviation increase in viral load was also associated with a 719±260 unit decrease in MFI (p=0.006). Additionally, a one kg increase in weight gained 28-42 dpi was associated with 250±101 lower MFI (p=0.014).

The GWAS discovered SNPs in the MHC class I region on chromosome 7 associated with tAb response. This region plays a crucial role in the host's ability to fight infection and harbors many genes associated with immune response. Furthermore, MHC class I genes are known to be involved in immune response to viral infection. This 1 Mb region was estimated to explain 30.5% of genetic variation, indicating the presence of a major QTL associated with IgG anti-N levels. One SNP in this region (DIAS0000349), located near the end of the 1 Mb window, explained all of the genetic variance that was captured by this window, and minimal linkage disequilibrium was observed among SNPs in this 1 Mb region.

Assessment of the effects of this SNP in ASReml indicated that heterozygotes had 4315±604 lower MFI than AA individuals (p<0.001). AB individuals gained 6.49±0.35 kg (n=115) from 28-42 dpi, while AA individuals only gained 5.71±0.29 kg (n=336), resulting in a difference of 0.78±0.29 kg of growth between 28 and 42 dpi (p=0.008) between AB and AA individuals. BB individuals were not used when comparing the effect of DIAS0000349 genotype on tAb response and WG because the number of BB individuals (n=5) was too small to get accurate estimates. This could be a QTL that is involved with susceptibility of piglets to the effects of the virus. This SNP did not have a significant effect on VL, REB, or nAb response, suggesting that this may be a QTL for general antibody response to viral infection.

These results suggest that the MHC may be an appropriate region for selecting for increased resistance or reduced susceptibility to viral infection. Haplotype analysis in the MHC may allow for a better understanding of the variability in this region that is driving these differences in immune response.

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